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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,808	12/03/2004	Francoise Bono	SSL0093-2 US PCT	5236

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ROSS J. OEHLER
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
LEESER, ERICH A	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
05/02/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,808	BONO ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-3-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6 and 10-16 are pending and under examination.

Priority

2. Acknowledgment is made that this application is a 371 of PCT/FR03/01686, filed on June 5, 2003, which claims foreign priority to application FRANCE 02/07001, filed on June 7, 2002.

Information Disclosure Statement

3. The references cited in the IDS, dated April 21, 2005, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6 and 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making solvates of the claimed invention. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working

examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The nature of the invention:

5. The invention is drawn to compounds of formula (I) (and processes for making and methods for using same), "or an acid addition salt, hydrate or solvate thereof." The specification is not adequately enabled to show how to make solvates of compounds of formula (I). The specification on page 24 recites: "The compounds of formula (I) may also exist in the form of hydrates or solvates, specifically in the form of associations or combinations with one or more molecules of water or with a solvent. Such hydrates or solvates also form part of the invention," but there is no enablement of such compounds.

6. The compounds of formula (I) embrace piperazinylacylpiperidine derivatives substituted with variable groups R_1 to R_{17}.

7. Even a cursory calculation of the number of compounds embraced in the instant formula (I) would result in perhaps thousands of compounds. This is of course far more compounds than the specification enables one skilled in the art to make. Thus, the genus embraced in claim 1 is too large and there is no teaching of any solvate of this large genus.

The state of the prior art:

8. A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its*

Applications, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

The predictability or lack thereof in the art:

9. For the reasons stated *supra*, the solvates as applied to the above-mentioned compounds claimed by the Applicant are not art-recognized compounds and hence there should be an enabling disclosure in the specification with working example(s).

The amount of direction or guidance present:

10. Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvates of the instant compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that the instant compounds formed solvates. Hence it is clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance.

The presence or absence of working examples:

11. There is no working example of any solvate formed. These cannot be simply willed into existence. "The specification purports to teach, with over fifty examples, the preparation of the

claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that solvates of these compounds exist and therefore can be made.

The breadth of the claims:

12. The breadth of the claims include all of the perhaps thousands of compounds of formula (I) of claim 1 as well as the presently unknown list of potential solvate derivatives embraced by these terms. The term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the solvates of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The quantity of experimentation needed

13. The specification has insufficient support, as noted *supra*, for the desired solvates of the compounds of formula (I). As noted above, the genus embraces perhaps thousands of compounds and hence the breadth of the claims is broad. The quantity of experimentation

needed would be an undue burden on one skilled in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated *supra*. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvates of the compounds of formula (I) embraced in the instant claims.

14. In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

15. Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to treat *all* central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures; bone diseases using a compound of formula (1) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

16. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the

inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

17. The instant invention is drawn to piperazinylacylpiperidine derivatives substituted with variable groups R_1 to R_{17}, including methods of treating central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures; bone diseases using a compound of formula (1).

The state of the prior art:

18. The prior art at the time the invention was made points away from enablement of Applicant's method claims, "[t]he use of neuronal growth factors in the treatment of neurodegenerative diseases, such as cerebral ischemia and the AIDS dementia complex, may prove much more effective if the elevated expression of TNF-α in these disorders is neutralized." Venters, H.D., et al., *Tumor Necrosis Factor-α Induces Neuronal Death by Silencing Survival Signals Generated by the Type I Insulin-like Growth Factor Receptor*, Annals New York Academy of Sciences, 917(1) 210-220 (2000). There is no evidence; however, that Applicant's claimed compounds in any way neutralize the elevated expression of TNF-α in the claimed treatment of central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve

and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures; or bone diseases.

The predictability in the art:

19. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of formula (I) would be useful for treating *all* central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures and bone diseases.

Amount of guidance/working examples:

20. The only example in the specification showing the activity of the binding of I-NGF to the p75 receptor is found on pages 80-81 of the specification. The included information; however, does not definitely prove that the instant compounds can be used for treating all central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers;

tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures; bone diseases using a compound of formula (I) to a subject in need thereof.

The breadth of the claims:

21. The instant invention is drawn to methods of treating central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures; bone diseases using a compound of formula (I) to a subject in need thereof.

The quantity of undue experimentation needed:

22. Since the guidance and teaching provided by the specification is insufficient for treating all central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures and bone diseases using a compound of formula (I) to a subject in need thereof, one of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

The level of the skill in the art:

23. The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed

for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

24. Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to use the compounds of formula (I) for treating all central or peripheral neurodegenerative diseases; amyotrophic lateral sclerosis, multiple sclerosis; cardiovascular conditions; peripheral neuropathies; damage to the optic nerve and to the retina; spinal cord trauma and cranial trauma; atherosclerosis; stenoses; cicatrisation; alopecia; cancers; tumors; metastases; leukemias; chronic neuropathic and inflammatory pain; autoimmune diseases, bone fractures; and bone diseases by administering a pharmaceutical composition to a subject in need thereof without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claims 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected if it is dependent on a rejected claim and shares the same indefiniteness.

(a) Claims 3-4 are rejected because they use the relative claim language, "these functions may be protected." This claim language is indefinite because one of skill in the art would not necessarily know or realize the scope of the claim, or know how to protect the functions in the claimed process step. Clarification is required.

(b) Claims 3-4 are rejected because they use the relative claim language, "where appropriate." This claim language is indefinite because one of skill in the art would not necessarily know or realize the scope of the claim, or know when it would be appropriate to deprotect the hydroxyl or amine functions present in R_3 in the claimed process step. Clarification is required to obviate this rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

EL

Erich A. Leeser
Assistant Examiner

Zachary C. Tucker
Primary Examiner